

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Schuetz C, Huck K, Gudowius S, et al. An immunodeficiency disease with RAG mutations and granulomas. *N Engl J Med* 2008;358:2030-8.

Supplementary Table 1: Immunophenotyping and T-cell clonality of the granulomatous lesions

	Patient 1 (compound heterozygeous RAG1 mutation)	Patient 2 (compound heterozygeous RAG1 mutation)	Patient 3 (compound heterozygeous RAG2 mutation)
Lymphocytes			
T cells (CD3)	+	+	+
CD4	-	-	-
CD8	+	+	+
clonality*	monoclonal	polyclonal	polyclonal
B cells (CD79a)	-	-	-
Epitheloid cells (CD68)	+	+	+

* TCR- γ gene rearrangements by semi-nested multiplex PCR

Supplemental Table 2. Overview of pathogen search in biopsy materials and blood (staining, culture, PCR, electron microscopy, serology)

Tests in biopsy material	<i>Patient 1</i>	<i>Patient 2</i>		<i>Patient 3</i>	
	skin	skin	lung/BAL	spleen	BAL
<i>staining</i>					
Gram stain	negative	negative	negative	negative	negative
Ziehl-Neelsen/Auramin staining (mycobacteria)	negative	negative	negative	negative	negative
PAS/Grokott (fungi)	negative	negative	negative	negative	negative
Whartin-Starry (spirochetes, bartonella)	n.d.	negative	n.d.	n.d.	n.d.
<i>culture</i>					
bacterial culture	negative	negative	n.d.	negative	negative
M. tuberculosis	negative	negative	n.d.	negative	negative
<i>PCR</i>					
M. tuberculosis	negative	negative	negative	negative	negative
Atypical mycobacteria	n.d.	negative	n.d.	n.d.	n.d.
Trophoeryema whippelii	negative	negative	n.d.	negative	n.d.
Leishmania	n.d.	negative	n.d.	n.d.	n.d.
Bartonella quintana und henselae	n.d.	negative	n.d.	n.d.	n.d.
Mycoplasma pneum.	n.d.	n.d.	n.d.	n.d.	negative
Chlamydia pneum.	n.d.	n.d.	negative	n.d.	negative
Legionella pneumoph.	n.d.	n.d.	negative	n.d.	negative
Pneumocystis carinii	n.d.	n.d.	negative	n.d.	n.d.
HSV-1	n.d.	negative	negative	n.d.	n.d.
VZV	n.d.	negative	n.d.	n.d.	n.d.
CMV	n.d.	negative	negative	negative	negative
HHV-6	n.d.	n.d.	negative	negative	negative
Parvovirus B19	n.d.	n.d.	negative	negative	negative
Adenovirus	n.d.	n.d.	negative	negative	negative
EBV	n.d.	n.d.	negative	239 K/ μ g DNA	405 K/ μ g DNA
Parapox virus	n.d.	negative	n.d.	n.d.	n.d.
<i>Electron microscopy</i>					
Parapoxvirus	n.d.	negative		n.d.	
Blood test s					
<i>serology</i>					
Borrelia burgdorferi ELISA	negative	n.d.		negative	
Borrelia burgdorferi Western Blot	negative	n.d.		negative	
<i>PCR</i>					
HBV	n.d.	negative		n.d.	
HCV	n.d.	negative		n.d.	
HIV	negative	negative		n.d.	
CMV	negative	negative		negative	
EBV	intermittently positive with undulating low copy number	intermittently positive with low copy number		intermittently positive with low copy nb.	
HHV-6	intermittently positive with low copy number	intermittently positive with low copy number		negative	
HSV-1/2	n.d.	negative		n.d.	
Parvovirus B19	negative	n.d.		negative	
Adenovirus	negative	n.d.		negative	

Supplemental Table 3 Familial distribution of *RAG* mutations

	gene	allele 1 (mother)	allele 2 (father)
Patient 1	RAG1	R314W	R507W/R737H
Patient 2*	RAG1	R778Q or R975W *	R778Q or R975W *
Patient 3**	RAG2	G451A	T77N

* *RAG* Genotype of the parents of patient 2 and sibling of patient 2 was not determined

** *RAG* Genotype of the half siblings of patient3 was not determined

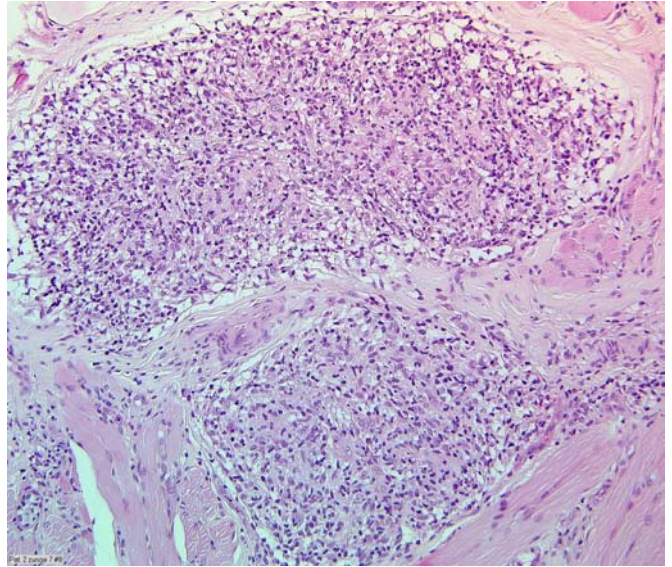
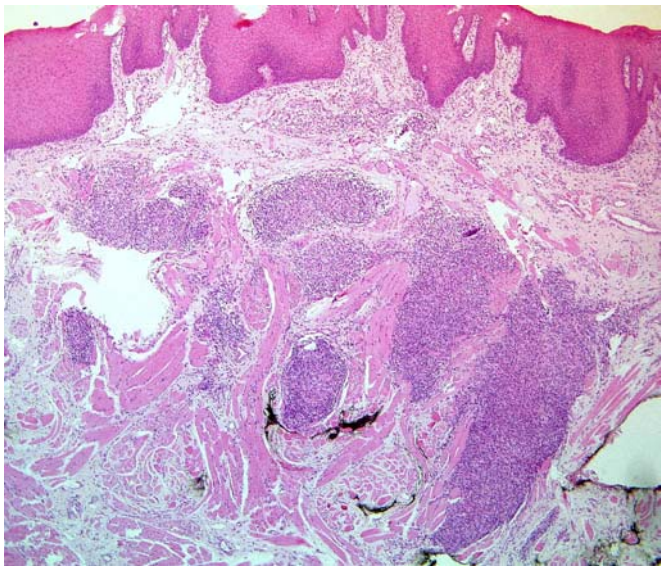


Figure 1 b. Upper panel: skin ulcerations of face and left knee in patient 2 without inflammatory activity showing skin contraction through scarring

Figure 1 b. Lower panel: Histopathology of tongue lesion in patient 2 showing nodular collections of epithelioid cells (left) surrounded by moderately dense lymphocytic infiltrate with some neutrophils (right). No necrosis was present.

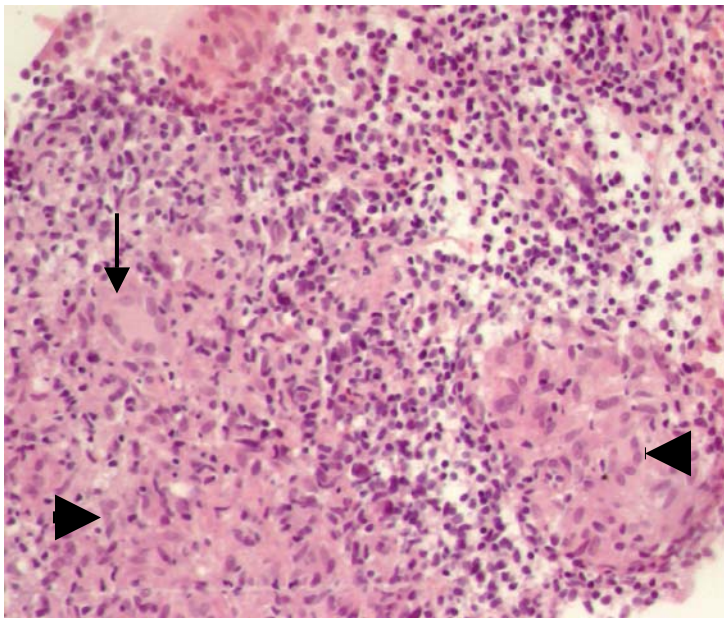
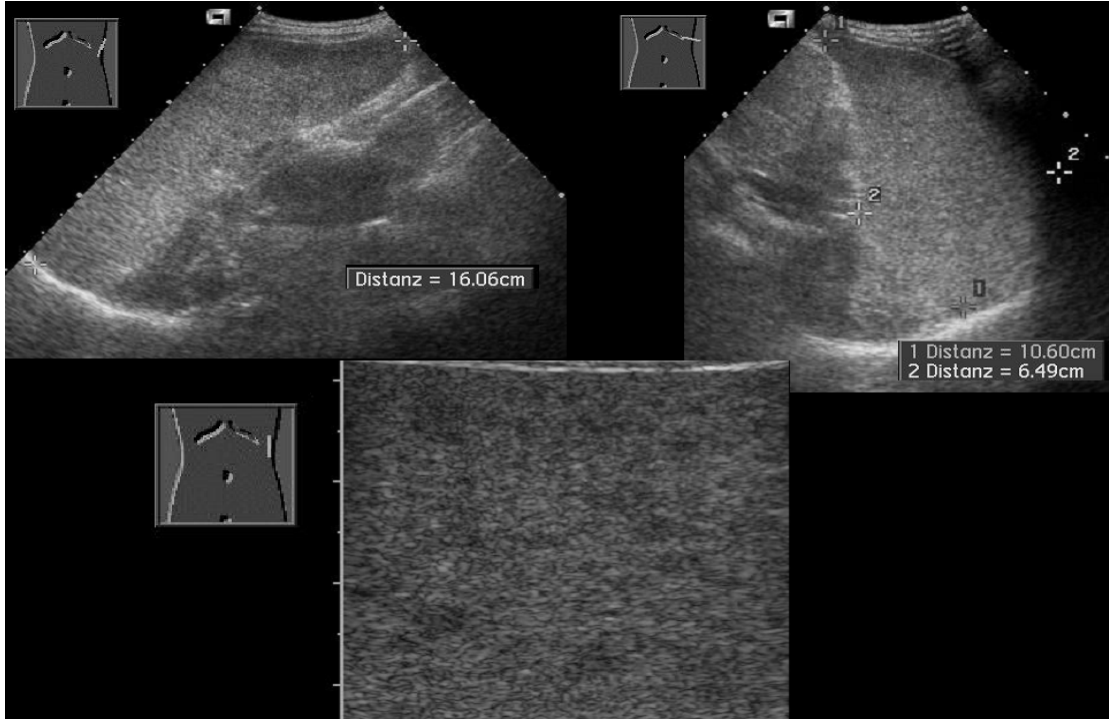


Figure 1c. Upper panel: Ultrasound of the spleen in *patient 3*: upper row left: longitudinal view, on the right transversal view; zoomed image taken with a linear array: gross enlargement of the spleen with a diffuse spread of small hypoechoic lesions.

Figure 1 c. Lower panel: Histopathology of spleen lesion showing nodular collections of epithelioid cells (arrows heads) surrounded by lymphocytic infiltrate with some neutrophils. Some of the epithelioid cells are multinucleated (arrow).